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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,746	06/22/1999	GREGORY M. GLENN	PM-254811	9348

7590 06/03/2003

Gary R Tanigawa
Nixon & Vanderhye P C
1100 North Glebe Road 8th Floor
Arlington, VA 22201-4714

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/337,746	Applicant(s) Glenn et al.
	Examiner G.R. Ewoldt, Ph.D.	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *2/12/03 and 3/05/03*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-42, 53-57, 59-63, and 65-70* is/are pending in the application.

4a) Of the above, claim(s) *70* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-42, 53-57, 59-63, and 65-69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *29*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. The amendment and remarks, filed 2/12/03, have been entered.

2. Claims 1-42, 53-57, 59-63, and 65-69 are being acted upon.

3. In view of Applicant's amendment and response, filed 3/05/03, only the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-42, 53-57, 59-63, and 65-69 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a method for transcutaneous immunization (TCI) comprising applying a formulation that does not include a heterologous adjuvant to intact skin, said formulation consisting of cholera toxin (CT), LT, or *Pseudomonas exotoxin A* (ETA), to hydrated skin does not reasonably provide enablement for,

B) a method for TCI comprising activating at least one antigen presenting cell underlying where the formulation's site of application,

C) a method for TCI comprising an APC wherein the APC is a Langerhans cell,

D)a method for TCI comprising applying an antigen in whole cell form,

E)a method for TCI comprising applying an antigen comprising a viral particle or virion,

F)a method for TCI comprising applying diphtheria toxin (DT),

G)a method for TCI wherein the induced immune response recognizes a lipopolysaccharide (LPS).

H)a method for TCI wherein the induced response recognizes influenza virus hemagglutinin (HA), influenza virus nucleoprotein

(NP), Hemophilus influenza B polysaccharide conjugate (Hib-PS), and *Escherichia coli* colonization factor CS6.

I)a method for TCI wherein underlying endosomes or lysosomes are lysed, for the reasons of record as set forth in Papers No. 19 and 24, mailed 12/04/01 and 8/06/02, respectively.

Applicant's arguments, filed 2/12/03, have been fully considered but they are not persuasive. Applicant has addressed only the rejection regarding a method for TCI comprising applying a formulation comprised of an antigen, wherein said formulation does not include a heterologous adjuvant to intact skin (previously Ground A). In view of Applicant's amending of the claims, said ground of rejection has been withdrawn. Grounds B-I and the requirement of hydrated skin remain.

6. The rejection of Claim 58 for lack of adequate written description has been withdrawn.

7. The following are new grounds for rejection.

8. Claims 1-42, 53-57, 59-63, and 65-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a method for transcutaneous immunization (TCI) comprising applying a formulation that does not include a heterologous adjuvant to intact skin, said formulation consisting of cholera toxin (CT), LT, or *Pseudomonas exotoxin A* (ETA), to hydrated skin does not reasonably provide enablement for,

a method for transcutaneous immunization (TCI) comprising applying a formulation consisting of genetically modified ADP-ribosylating exotoxins.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427

F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts are such that no methods of inducing an immune response, comprising the providing of all of the genetically modified ADP-ribosylating exotoxins that would be encompassed by the instant invention as broadly claimed, are currently known.

It is noted that the jumbo specification provides only a superficial discussion of the genetically modified ADP-ribosylating exotoxins of the claims. Indeed, the entire disclosure consists of the following:

"To overcome the problem of the toxicity of the toxins, (e.g., diphtheria toxin is known to be so toxic that one molecule can kill a cell) and to overcome the difficulty of working with such potent toxins as tetanus, several workers have taken a recombinant approach to producing genetically altered toxoids. This is based on inactivating the catalytic activity of the ADP-ribosyl transferase by genetic deletion. These toxins retain the binding capabilities, but lack the toxicity, of the natural toxins. This approach is described by Burnette et al. (1994), Rappuoli et al. (1995), Dickinson and Clements (1995), and Rappuoli et al. (1996). Such genetically toxoided exotoxins could be useful for transcutaneous immunization system in that they would not create a safety concern as the toxoids would not be considered toxic."

Said disclosure cannot be considered to teach one of skill in the art how to make and use all of the genetically modified ADP-ribosylating exotoxins that would be encompassed by the claims. Note that the term is not even defined. Accordingly, said term must be considered to encompass fragments of genetically modified ADP-ribosylating exotoxins as small as single amino acids. Given the admittedly unexpected nature of the method of the instant claims, the generation of an immune response employing all of the genetically modified ADP-

ribosylating exotoxins encompassed by the instant claims must be considered to be highly unpredictable. Said unpredictability would then be considered to require undue experimentation.

Applicant's response, submitted 2/12/03, indicates that Examples 31 and 35 employ genetically modified ADP-ribosylating exotoxins. A review of the examples, however, reveals a disclosure insufficient to be considered to be enabling, given the breadth of the claims. Example 31 merely discloses that "tetanus fragment C" was used; nothing about said "fragment" is disclosed. Example 35 discloses that two toxins, apparently identified only by laboratory designations, "LTK63, an enzymatically inactive LT derivative, and LTR72, an LT derivative which retains 0.6% of the unmodified LT's enzymatic activity", were employed. These disclosures cannot be considered to be adequate to teach one of skill in the art how to make and use the genetically modified ADP-ribosylating exotoxins encompassed by the claims.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples (i.e., any working examples in which specific an identified genetically modified ADP-ribosylating exotoxins are employed), the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-42, 53-57, 59-63, and 65-69 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of "genetically modified ADP-ribosylating exotoxins", other than cholera toxin B subunit. The brief disclosure at page 34 of the specification (set forth

above) discloses no species of the claimed genus other than the cholera toxin B subunit. Also as set forth above, absent a specific definition of "genetically modified ADP-ribosylating exotoxins", said exotoxins must be considered to include even single amino acids. Accordingly, the disclosure of a single species is insufficient to describe an essentially unlimited genus. Again, it is noted that Examples 31 and 35 appear to employ "genetically modified ADP-ribosylating exotoxins", however, they are not adequately described. In fact, they are not actually described at all. In particular, Example 35 appears to employ antigens/adjuvants identified only by laboratory designations. Said designations do not provide an adequate written description for the "genetically modified ADP-ribosylating exotoxins" of the claims. Accordingly, one of skill in the art must conclude that the specification fails to disclose an adequate written description or a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321c may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1-42, 53-57, 59-63, and 65-69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 3-35, 50-77, and 79-111 of copending Application No. 09/266,803. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the instant application recite a method of TCI comprising employing an ADP-ribosylating exotoxin to induce an immune response. The claims of the '803 application recite a method of inducing an immune response

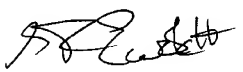
employing a generic ADP-ribosylating exotoxin (Claim 30-33) or specific ADP-ribosylating exotoxins(Claims 22-26). The methods are therefore not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Technology Center 1600 at 703-872-9306 (before final) and 703-872-9307 (after final).



G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
June 2, 2003